

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 099179396262	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. PCT/CA2007/001935	International filing date ( <i>day/month/year</i> ) 26 October 2007 (26.10.2007)	Priority date ( <i>day/month/year</i> ) 27 October 2006 (27.10.2006)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant MOUNT SINAI HOSPITAL			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input checked="" type="checkbox"/> | Box No. II   | Priority  |
| <input checked="" type="checkbox"/> | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input checked="" type="checkbox"/> | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/>            | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 28 April 2009 (28.04.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  <b>Athina Nickitas-Etienne</b>
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

**CORRECTED VERSION**

**PCT**

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:  
**MCCARTHY TETRAULT LLP**  
Box 48, Suite 4700  
Toronto Dominion Bank Tower  
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TORONTO, Ontario  
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Date of mailing 22 February 2008 (22-02-2008)  
(day/month/year)

Applicant's or agent's file reference  
099179396262

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
**PCT/CA2007/001935**

International filing date (day/month/year)  
26 October 2007 (26-10-2007)

Priority date (day/month/year)  
27 October 2006 (27-10-2006)

International Patent Classification (IPC) or both national classification and IPC  
IPC: **C40B 40/10** (2006.01), **A61K 49/00** (2006.01), **C07K 14/47** (2006.01), **C07K 14/52** (2006.01), **C07K 14/705** (2006.01), **C07K 14/775** (2006.01) (more IPCs on the last page)

Applicant  
**MOUNT SINAI HOSPITAL ET AL**

1. This opinion contains indications relating to the following items :

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> Box No. I    | Basis of the opinion   |
| <input checked="" type="checkbox"/> Box No. II   | Priority   |
| <input checked="" type="checkbox"/> Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability   |
| <input checked="" type="checkbox"/> Box No. IV   | Lack of unity of invention   |
| <input checked="" type="checkbox"/> Box No. V    | Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI              | Certain documents cited  |
| <input type="checkbox"/> Box No. VII             | Certain defects in the international application   |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application  |

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA  
Canadian Intellectual Property Office  
Place du Portage I, C114 - 1st Floor, Box PCT  
50 Victoria Street  
Gatineau, Quebec K1A 0C9  
Facsimile No.: 001-819-953-2476

Date of completion of this opinion  
06 February 2008 (06-02-2008)

Authorized officer  
**Riad Qanbar 819- 934-7937**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

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PCT/CA2007/001935

**Box No. I                      Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:  
  
    ☒ the international application in the language in which it was filed  
  
    ☐ a translation of the international application into \_\_\_\_\_, which is the language of a  
        translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified  
    to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed  
    invention, this opinion has been established on the basis of :
  - a. type of material  
  
        ☒ a sequence listing  
  
        ☒ table(s) related to the sequence listing
  - b. format of material  
  
        ☒ on paper  
  
        ☒ in electronic form
  - c. time of filing/furnishing  
  
        ☒ contained in the international application as filed.  
  
        ☐ filed together with the international application in electronic form  
  
        ☒ furnished subsequently to this Authority for the purposes of search.
4. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has  
    been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in  
    the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments :

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INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. II**      **Priority**

- 1    ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
  
- 2    ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
  
3. Additional observations, if necessary :

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INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. III      Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

☐ the entire international application

☒ claim Nos.      25, 27-32

because:

☒ the said international application, or the said claim Nos.      25, 27-32      relate to the following  
subject matter which does not require an international search (*specify*) :

Claim 25 is directed to a method for treatment of the human or animal body by surgery or therapy, whereas claims 27-32 are directed to diagnostic methods that encompass a method of medical treatment because the diagnostic agents used in these claims may impart a therapeutic benefit. Even though under Rule 67.1(iv) of the PCT this Authority is not required to offer a written opinion on this subject matter, a search was performed and a written opinion is offered based on the alleged use of the product defined in the aforementioned claims.

☐ the description, claims or drawings (*indicate particular elements below*) or said claim Nos.  
are so unclear that no meaningful opinion could be formed (*specify*) :

☐ the claims, or said claims Nos.      are so inadequately supported  
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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**Box No. IV      Lack of unity of invention**

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit :
- ☐ paid additional fees
  - ☐ paid additional fees under protest and, where applicable, the protest fee
  - ☐ paid additional fees under protest but the applicable protest fee was not paid
  - ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with
  - ☒ not complied with for the following reasons :

The claims are directed to a plurality of inventive concepts as follows:

Group 1 - Claims 1-32, 34-41 (partially) are directed to methods using whey acid protein four-disulfide core domain (WFDC2) as a marker for endometrial disease, and sets of markers and kits containing the same;

Group 2 - Claims 1, 3, 4, 8, 29-32, 34-39 (partially) and 33 (completely) are directed to methods using whey acid protein four-disulfide core domain (WFDC2) as a marker for endometrial phase and sets of markers containing the same;

Groups 3, 5, 7, 9, and 11 - Claims 1-32, 34-41 (partially) are directed to methods using clusterin (Group 3), mucin 5B (Group 5), leucine aminopeptidase 3 (Group 7), gelsolin-like capping protein (Group 9) or progesterone-associated endometrial protein (Group 11) as a marker for endometrial disease, and sets of markers and kits containing the same; and

Groups 4, 6, 8, 10 and 12 - Claims 1, 3, 4, 8, 29-32, 34-39 (partially) are directed to methods using clusterin (Group 4), mucin 5B (Group 6), leucine aminopeptidase 3 (Group 8), gelsolin-like capping protein (Group 10) or progesterone-associated endometrial protein (Group 12) as a marker for endometrial phase and sets of markers containing the same.

The claims must be limited to one inventive concept as set out in Rule 13 of the PCT. An a posteriori analysis has concluded that biomarkers associated with endometrial cancer are known in the art and thus cannot serve as a novel and inventive feature uniting the subject matter of the instant application. Individual markers (Galgano et al; Zierau et al; Hebbar et al; Li et al), lists of markers that exhibit altered expression levels in endometrial cancer (WO 02/09573; Mutter et al; Desouza et al, J. Proteome Res.; WO 2005/061725 ), and true combinations of markers where the diagnostic value of the combination is superior to that of the individual markers (Ferguson et al; Reid-Nicholson et al) have been previously described. In view of the aforementioned prior art documents, each endometrial marker or specific combination of markers is to be assessed as an independent alleged invention.

Further, endometrial phase markers are known in the art (Ace et al; Lalitkumar et al; Desouza et al, Proteomics, 2005). A given endometrium-associated marker that serves as an endometrial cancer biomarker does not necessarily serve as an endometrial phase biomarker and vice versa. It follows that, because being an endometrial phase biomarker is independent of being an endometrial cancer biomarker, the utility of the claimed biomarker is another basis for the division of the subject matter of the instant claims.

4. Consequently, this opinion has been established in respect of the following parts of the international application :
- ☒ all parts
  - ☐ the parts relating to claim Nos.

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**Box No. V**      **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Claims <u>32, 36-38</u>	YES
	Claims <u>1-31, 33-35, 39-41</u>	NO
Inventive step (IS)	Claims <u>36</u>	YES
	Claims <u>1-35, 37-41</u>	NO
Industrial applicability (IA)	Claims <u>1-41</u>	YES
	Claims <u>None</u>	NO

**2. Citations and explanations :**

Reference is made to the following documents:

- D1: ACE, C.I. et al. "Microarray Profiling of Progesterone-Regulated Endometrial Genes During the Rhesus Monkey Secretory Phase", *Reprod. Biol. Endocrinol.*, 2004, Vol.2, pages 54-62.
- D2: GALGANO, M.T. et al. "Comprehensive Analysis of HE4 Expression in Normal and Malignant Human Tissues", *Mod. Pathol.*, June 2006, Vol.19, No.6, pages 847-853.
- D3: ZIERAU, O. et al. "Tamoxifen Exerts Agonistic Effects on Clusterin and Complement C3 Gene Expression in RUCA-I Primary Xenografts and Metastases But Not Normal Uterus", *Endocr. Relat. Cancer*, 2004, Vol.11, No.4, pages 823-830.
- D4: HEBBAR, V. et al. "Differential Expression of MUC Genes in Endometrial and Cervical Tissues and Tumors", *BMC Cancer*, 2005, Vol.5, pages 124-135.
- D5: LALITKUMAR, P.G.L. et al. "Placental Protein 14 in Endometrium During Menstrual Cycle and Effect of Early Luteal Phase Mifepristone Administration on its Expression in Implantation Stage Endometrium in the Rhesus Monkey", *Hum. Reprod.*, 1998, Vol.13, No.12, pages 3478-3486.
- D6: LI, T.C. et al. "Is the Measurement of Placental Protein 14 and CA-125 in Plasma and Uterine Flushings Useful in the Evaluation of Peri-Menopausal and Post-Menopausal Bleeding?", *Hum. Reprod.* 1998, Vol.13, No.10, pages 2895-2901.
- D7: MUTTER, G.L. et al. "Global Expression Changes of Constitutive and Hormonally Regulated Genes During Endometrial Neoplastic Transformation", *Gynecol. Oncol.*, 2001, Vol.83, No.2, pages 177-185.
- D8: WO 02/09573 A2 (MUTTER, G.L. [US]) 7 February 2002.
- D9: DESOUZA, L. et al. "Proteomic Analysis of the Proliferative and Secretory Phases of the Human Endometrium: Protein Identification and Differential Protein Expression", *Proteomics*, 2005, Vol.5, No.1, pages 270-281.
- D10: WO 2005/061725 A1 (COLGAN, T.J. [CA/CA]) 7 July 2005.
- D11: DESOUZA, L. et al. "Search for Cancer Markers from Endometrial Tissues Using Differentially Labeled Tags iTRAQ and cICAT with Multidimensional Liquid Chromatography and Tandem Mass Spectrometry", *J. Proteome Res.*, 2005, Vol.4, No.2, pages 377-386.

The application relates to biomarkers associated with endometrial phase and their use in determining the receptivity of uterine endometrium and to biomarkers associated with endometrial cancer and their use for diagnosing and predicting the prognosis of the disease.

(Continued in Supplemental Box)

**WRITTEN OPINION OF THE  
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**Box No. VIII      Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claims 1-20, 22-24, 29-32 and 33 are broader in scope than the teaching of the description. To comply with Article 6 of the PCT the claims must specify that the sample is an endometrial tissue sample. There is no substantive support in the description for altered levels of any of the proteins of Table 1 in any sample source other than endometrial tissue.

Claims 1-4, 8-16, 27-32, and 34-41 are broader in scope than the teaching of the description. To comply with Article 6 of the PCT the claims must specify that the endometrial disease is endometrial cancer. No other endometrial disease is substantively supported by the description.

Claims 1, 3, 4, 8, 9, and 29-39 encompass embodiments which cannot operate, and therefore does not comply with Article 6 of the PCT. Data presented in Table 3 raise serious doubts concerning the usefulness of any of the proteins in Table 1, other than PP14, as an indicator of endometrial phase. The difference in the average value of these markers between proliferative and secretory endometria is not likely to be statistically significant.

Claims 2-41 are broader in scope than the teaching of the description and do not comply with Article 6 of the PCT. There is no substantive evidence in the description for the utility of any of the proteins in Table 1, singly or in combination, for the diagnosis of endometrial cancer. Even though the statistical averages of the levels of some of the proteins in Table 1 may show differences between malignant and normal endometrial samples, the individual values for any given protein are spread over a broad range in both normal and cancerous tissue (Table 3). Therefore, despite the correlation of statistical average of given protein levels with endometrial cancer, the individual expression levels of any one of the proteins given in Table 1 is unlikely to be sufficient for diagnosing, let alone predicting the prognosis of, endometrial cancer. Nor does the description show it to be sufficient. While combinations of markers may be of potential diagnostic value, the only combination tested in the description does not include as a component any of the proteins listed in Table 1 (see Table 5 and Fig. 1).

Claims 10-18 are broader in scope than the teaching of the description. To comply with Article 6 of the PCT the aforementioned claims must specify that measuring the level of, and not merely detecting, the specified compounds is required for the methods of these claims. None of the markers in Table 1 is absent in normal endometrial tissue while expressed in cancerous states or vice versa. Therefore, detection, which is only an indicator of the presence or absence of a given compound, is not sufficient to make any conclusions regarding the cancer status of the tissue.

Claims 27 and 28 are broader in scope than the teaching of the description and do not comply with Article 6 of the PCT. Even though agents that bind the markers of Table I are disclosed in the description, the ability of these agents to bind in vivo to cancer cells so as to be useful in diagnostic imaging in live subjects is questionable. For example, for antibodies to be of use, they need to bind an epitope of a marker protein expressed at the cell surface. Similarly, the utility of nucleic acids is hampered by the need of denaturation for hybridisation to occur. The description offers no indication of whether and how imaging can be done with the disclosed agents.

Claims 1-3, 10, 27-32, 34, 40 and 41 are indefinite and do not comply with Article 6 of the PCT. The inclusion of "endometrial markers" causes ambiguity. The proteins in Table 1 are expressed in many tissues and are not specific to the endometrium so as to be called endometrial markers. Clarity may be enhanced by referring to these proteins as "endometrial cancer markers" or "endometrial phase markers", as appropriate.

Claims 1, 2, 5, 10, 17-27, 34, 40 and 41 do not comply with Rule 6.2(a) of the PCT. Reference is made to the description (Table 1 in claims 1, 2, 5, 10, 17-27, 34, 40 and 41 and Table 2 in claim 34) for completeness and clarity, rather than claiming the subject matter in explicit terms. Table 1 has only 6 elements, which can be easily incorporated in the text of the claims.

Claim 1 is indefinite and does not comply with Article 6 of the PCT. The inclusion of "detecting in proteins extracted....polynucleotides" causes ambiguity. It is not clear how polynucleotides can be detected in extracted proteins.

Claims 6 and 7 have a grammatical error, namely, the subject and verb do not match in "wherein the level of endometrial cancer markers are...".

Claim 16 is indefinite and does not comply with Article 6 of the PCT. There is no step "(c)" in the method outlined in this claim, even though steps (d) and (e) are present.

(Continued in Supplemental Box)

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V (Part 1 of 2)

D1 discloses lists of biomarkers associated with endometrial phase and therefore endometrial receptivity. These biomarkers include whey acidic protein four disulfide core domain 2 (WFDC2) and clusterin (Table 2 - Additional File 2).

D2 discloses the association of WFDC2, which is also known as human epididymis protein 4 (HE4), with endometrial cancer (Fig.4) and its use as a diagnostic biomarker.

D3 discloses the association between clusterin over-expression in breast cancer patients treated with tamoxifen and the increased incidence of endometrial cancer in these patients, thus highlighting the association between clusterin expression and endometrial cancer.

D4 discloses the association of the overexpression of mucins, particularly mucin 5B, with endometrial neoplastic growth.

D5 discloses the association of progestagen-associated endometrial protein (PAEP), also known as placental protein 14 (PP14), with endometrial phase, and thus its usefulness in assessing uterine receptivity.

D6 discloses the utility of measuring PP14 levels in diagnosing endometrial adenocarcinoma in post-menopausal women.

D7 discloses a list of biomarkers the level of expression of which is indicative of endometrial cancer. The list includes PAEP.

D8 discloses a list of biomarkers for diagnosing, predicting the outcomes of, monitoring the progression of, and assessing the treatment of endometrial cancers. The list includes PP14.

D9 discloses proteins that are differentially expressed in the secretory vs proliferative endometrial phases. PAEP, glutamate receptor subunit zeta1, FRAT1, and myosin light chain kinase 2 are among these proteins.

D10 discloses proteins whose level of expression is indicative of endometrial phase or endometrial cancer. These proteins (see Tables 1, and 4 to 6) include chaperonin 10, alpha-1- antitrypsin precursor, creatine kinase B chain, pyruvate kinase M1 or M2, transgelin, macrophage migration inhibitory factor, and polymeric immunoglobulin receptor precursor I, as well as other proteins that appear in Table 2 of the instant application.

D11 discloses proteins differentially expressed in endometrial cancers. These proteins include chaperonin 10, alpha-1- antitrypsin precursor, creatine kinase B chain, pyruvate kinase M1 or M2, and transgelin (Table 1), as well as macrophage migration inhibitory factor and polymeric immunoglobulin receptor precursor I, among others (Table 2).

**NOVELTY AND INVENTIVE STEP**

**Endometrial Phase Biomarkers:**

D1, D5, D9 and D10 individually describe biomarkers associated with endometrial phase. D1 discloses WFDC2 and clusterin; D5 and D9 disclose PAEP; whereas D9 and D10 disclose some of the optional markers recited in claim 33 of the instant application. Also disclosed are methods of determining endometrial phase, and hence uterine receptivity, by measuring the levels of the protein biomarkers (D5 and D9) or the levels of the polynucleotides encoding them (D1). Accordingly, claims 1, 3, 8, 29, 33-35 and 39 lack novelty over D1 and claims 1, 3, 4, 8 and 39 lack novelty over either D5 or D9. In addition, combining WFDC2 and clusterin of D1 with PAEP of either D5 or D9 in one set of markers is obvious because all three exhibit differential expression in association with endometrial phase. Therefore, claim 38 lacks an inventive step having regard to D1 in view of either D5 or D9. Claim 4 is obvious in view of D1 and common general knowledge because one skilled in the art would have had no difficulty measuring the amount of the biomarkers using antibodies instead of oligonucleotides as disclosed in D1.

**Endometrial Cancer Biomarkers:**

Each of D2-D4 and D6-D8 describes an endometrial cancer biomarker listed in Table 1 of the instant application, as well as a method of measuring the level of said marker and reagents necessary for this measurement. Therefore, independent claims 1, 2, 5, 10, 17, 18, 21, and 39 lack novelty over any one of the aforementioned documents. D2-D4, respectively, disclose WFDC2, clusterin and mucin 5B as endometrial cancer markers, thus compromising the novelty of claims 29 and 30 (D2-D4) as well as claim 31 (D3 and D4).

(Continued in next Supplemental Box)

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.  
PCT/CA2007/001935

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V ( Part 2 of 2)

D10 and D11 individually describe cancer markers that are not found in Table 1, but are recited in claims 37 and 38. Any combination of known endometrial cancer biomarkers and its use in methods of the instant application would have been obvious to one skilled in the art. Therefore, in the absence of a proven advantage for a given combination, combining known endometrial cancer biomarkers, such as two or more of the markers of any one of D2-D4 and D6-D8 and optionally including two or more other known endometrial cancer biomarkers, such as the ones disclosed by either D10 or D11, entails no inventive ingenuity. Accordingly, the method of claim 32, and the marker sets of claims 34, 35, 37, and 38 would have been obvious to one skilled in the art in view of the appropriate combination of documents D2-D4, D6-D8, D10 and D11 to match the biomarkers recited in the individual claims.

The detection methods described in D2-D4 and D6-D8 target proteins only (D6), nucleic acids only (D4 and D7) or both proteins and nucleic acids (D2, D3, and D8). Accordingly, claims 3, 4, 8, 9, 11-17, and 39-41 lack novelty over D8; claims 3, 4, 6, 8, 9, 15-17, and 39-41 are not novel in view of either D2 or D3; claims 3, 8, 9, 11-17 and 39-41 lack novelty over either D4 or D7 with D4 further compromising the novelty of claim 6 and D7 further compromising the novelty of claim 7; and claims 3, 4, 6, 8, 9, 39 and 40 lack novelty over D6. Further, since protein and nucleic acid detection methods are common knowledge in the art, any detection method steps mentioned in claims 3, 4, 8, 9, and 11-16 of the instant application but not specifically described in any of D2-D4 and D6-D8 would have been obvious to the skilled artisan. Also obvious is the quantification of nucleic acids instead of proteins for assessing marker expression, thus rendering the subject matter of claim 41 un inventive having regard to D6 and common general knowledge.

A link between a specific endometrial cancer biomarker from Table 1 and cancer grade/prognosis is described in D2 and D8. In addition, both D2 and D8 individually disclose the utility of said endometrial cancer biomarkers in inhibiting endometrial cancer. Therefore, novelty cannot be acknowledged for claim 25 in view of either D2 or D8. D8 further discloses methods for assessing endometrial cancer metastasis, methods for imaging of endometrial cancer, methods for assessing the efficacy of a test or therapeutic agent, and methods for selecting a cancer inhibitory agent, thus compromising the novelty of claims 19, 20, 22-24, 27 and 28. D3, which links the carcinogenicity of the drug tamoxifen to the over-expression of clusterin, destroys the novelty of claim 26.

One skilled in the art would have had no difficulty in applying known endometrial cancer biomarkers for various purposes utilising any number of methods, including any of the individual methods of claims 18-20 and 22-28. Since the description of the instant application does not provide exemplary support for any of the methods of said claims, methods that are recited in said claims but not specifically mentioned in any one of D2-D4 and D6-D8 are considered not to involve an inventive step in view of any one of D2-D4 and D6-D8 having regard to common general knowledge.

In view of the above, only claims 32 and 36-38 are found to comply with Article 33(2) of the PCT. Of these, claim 36 is found to comply with Article 33(3) of the PCT.

INDUSTRIAL APPLICABILITY

The subject matter of claims 1-41 is considered to be industrially applicable and thus complies with the requirements of Article 33(4) of the PCT.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
**PCT/CA2007/001935**

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box VIII - Certain observations on the international application

Claim 21 does not comply with Article 6 of the PCT for a number of reasons. Firstly, applicant is claiming a composition without fully defining it in the claim. A composition contains at least two components, but applicant has only defined one - an agent that binds to an endometrial cancer marker or hybridizes to a polynucleotide encoding the marker. Secondly, this single component is not defined distinctly and explicitly. The "agent that binds" is not defined beyond a statement of its desired function. Further, where the agent hybridises to a polynucleotide encoding a marker, the hybridisation conditions are not set forth. It is well known in the art that, depending on the exact hybridization and wash conditions used, nucleic acid molecules with different degrees of identity can be detected. Because the conditions are not defined in the claim 21, a person skilled in the art would not be able to determine if a given molecule having a certain degree of identity with the claimed sequence is encompassed or not by the definition of the above claim. Finally, the inclusion of "such marker" renders the scope of the claim indefinite because it nullifies the restriction of markers to the ones listed in Table 1.

Claim 22 is unclear and does not comply with Article 6 of the PCT. The inclusion of "wherein the endometrial cancer markers" results in ambiguity.

Claim 27 does not comply with Article 6 of the PCT. As currently formulated, this use claim could be interpreted to encompass a method of medical treatment because it includes a method step, namely, "injecting a subject".

Claim 28 is unclear and does not comply with Article 6 of the PCT. The double inclusion of any element renders the claims indefinite. The term "an endometrial marker" has already been defined previously in the claims and should therefore be referred to using a definite article.

Claims 29-33, 35 and 36 are indefinite and does not comply with Article 6 of the PCT. The abbreviations, "WAP" (claims 29, 30 and 35), "LAP3" (claims 30, 31, and 36), "CAP-G" (claims 30, 31, and 36), "WFDC2" (claims 32 and 33), and "GSK-3" (claim 33), are not defined as "whey acidic protein", "leucine aminopeptidase 3", "gelsolin-like actin capping protein", "whey acidic protein four domain core domain 2", and "glycogen synthase kinase-3", respectively. To avoid any ambiguity, abbreviations should be fully defined on their first occurrence in each claim, unless they have been defined in a claim upon which the claim containing the abbreviation depends.

Claims 29-32, 34, and 35 are unclear and do not comply with Article 6 of the PCT. The use of the expressions "comprise or consist of" (claim 29-32), "comprising or consisting of" (claim 34), "comprise or are selected from" (claim 35) attempts to give both broad and narrow meaning to the scope of the aforementioned claims.

Claims 29-32 are unclear and do not comply with Article 6 of the PCT. These claims refer to "a method according to any preceding claim", even though preceding claim 21 is not directed to a method.

Claims 29 and 33-35 are unclear and do not comply with Article 6 of the PCT. The use of the expressions "preferably" (claims 29 and 35), and "optionally" (claims 33 and 34) causes ambiguity. These expressions raise uncertainty as to the presence of the specific statement to which they relate.

Claims 29, 33, 35, and 36 are indefinite and does not comply with Article 6 of the PCT. The inclusion of and/or causes ambiguity.

Claims 29 and 35 are unclear and do not comply with Article 6 of the PCT. The protein "mucin" lacks a proper antecedent basis in claims 1-28 on which claim 29 depends and in claim 34 on which claim 35 depends. Claims 1-28 and 34 have reference to mucin 5B (in Table 1).

Claim 32 is unclear and does not comply with Article 6 of the PCT. The terms "pyruvate kinase M1/M2", "chaperonin 10", and " $\alpha$ -1 antitrypsin" lack a proper antecedent basis in claims 1-31 on which this claim depends.

Claim 35 does not comply with Article 6 of the PCT. The term "and/or" before the last element of the specified group causes a lack of clarity, as it is unknown whether the last element is part of said group or not.

Claim 38 is unclear and does not comply with Article 6 of the PCT. The last member of the list of components further included in the claimed set of markers should be preceded by "and" or "or". In addition, the inclusion of a feature in parentheses "(PAEP or PP14)" in this claim causes ambiguity.

(Continued in next Supplemental Box)

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
**PCT/CA2007/001935**

**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.

Continuation of : Supplemental Box 3 (Box VIII - Certain observations on the international application)

Claim 39 is unclear and does not comply with Article 6 of the PCT. The components of the claimed kit are not defined. In addition, this claim refers to "a method as claimed in any preceding claim", even though claims 21 and 34-38 are not directed to methods.

Claims 40 and 41 do not comply with Article 6 of the PCT. Applicant is claiming a kit without fully defining it in the claims. A kit contains at least two components, but applicant has only defined one.

The description does not comply with Article 5 of the PCT. The http internet address provided on page 97, line 21, and page 100, line 36, is not a static electronic file. The information disclosed in said file can change and therefore is not reliable. Therefore, a person skilled in the art is not fully enabled to practice the alleged invention of the present application.

The description does not comply with Article 5 of the PCT. All documents referred to in the description of an application must be available to the public. Reference to the document on page 19, line 18 must be deleted or replaced by its corresponding patent number or publication number.

The description does not comply with Article 5 of the PCT. The documents referred to on page 100, line 16, and page 101, line 12, is not fully identified and therefore not accessible by the public. A document so referred to should be identified by country, number and date for published patent documents, or by title, author, date, and source for non-patent documents.

Continuation of : International Patent Classification

*C07K 14/81* (2006.01) , *C12N 9/12* (2006.01) , *C12Q 1/00* (2006.01) , *C12Q 1/68* (2006.01) ,  
*C40B 30/00* (2006.01) , *C40B 30/04* (2006.01) , *G01N 33/53* (2006.01) , *G01N 33/574* (2006.01)

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2007/001935

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C40B 40/10** (2006.01) , **A61K 49/00** (2006.01) , **C07K 14/47** (2006.01) , **C07K 14/52** (2006.01) ,  
**C07K 14/705** (2006.01) , **C07K 14/775** (2006.01) (more IPCs on the last page)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**C40B 40/10** (2006.01), **A61K 49/00** (2006.01), **C07K 14/47** (2006.01), **C07K 14/52** (2006.01), **C07K 14/705** (2006.01), **C07K 14/775** (2006.01), **C07K 14/81** (2006.01), **C12N 9/12** (2006.01), **C12Q 1/00** (2006.01), **C12Q 1/68** (2006.01), **C40B 30/00** (2006.01), **C40B 30/04** (2006.01), **G01N 33/53** (2006.01), **G01N 33/574** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Databases: PubMed, Scopus, Delphion, Canadian Patent Database; Search terms: endometrial, endometrium, cancer, marker\*, WAP, WFDC2, HE4, clu, clusterin, Mucin 5B, Muc5B, leucine aminopeptidase, LAP3, macrophage capping protein, gelsolin-like capping protein, CAP-G, progesteragen-associated, PP14, PAEP, endometrial phase - in various combinations

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	ACE, C.I. et al. "Microarray Profiling of Progesterone-Regulated Endometrial Genes During the Rhesus Monkey Secretory Phase", Reprod. Biol. Endocrinol., 2004, Vol.2, pages 54-62, eISSN 1477-7827.	1, 3, 4, 8, 29, 33-35, 39 38
X — Y	GALGANO, M.T. et al. "Comprehensive Analysis of HE4 Expression in Normal and Malignant Human Tissues", Mod. Pathol., June 2006, Vol.19, No.6, pages 847-853, pISSN 0893-3952, eISSN 1530-0285.	1-6, 8-18, 21-30, 39-41 32, 34, 35, 37, 38
X — Y	ZIERAU, O. et al. "Tamoxifen Exerts Agonistic Effects on Clusterin and Complement C3 Gene Expression in RUCA-I Primary Xenografts and Metastases But Not Normal Uterus", Endocr. Relat. Cancer, 2004, Vol.11, No.4, pages 823-830, pISSN 1351-0088, eISSN 1479-6821.	1-6, 8-31, 39-41 32, 34, 35, 37, 38

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

04 January 2008 (04-01-2008)

Date of mailing of the international search report

22 February 2008 (22-02-2008)

Name and mailing address of the ISA/CA  
Canadian Intellectual Property Office  
Place du Portage I, C114 - 1st Floor, Box PCT  
50 Victoria Street  
Gatineau, Quebec K1A 0C9  
Facsimile No.: 001-819-953-2476

Authorized officer

Riad Qanbar 819- 934-7937

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/CA2007/001935**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 25 and 27 -32

because they relate to subject matter not required to be searched by this Authority, namely :

Claim 25 is directed to a method for treatment of the human or animal body by surgery or therapy, whereas claims 27-32 encompass a method of such medical treatment (diagnostic agents may carry a therapeutic benefit). Even though under Rule 39.1 (iv) of the PCT this Authority is not required to search this subject matter, a search was done based on the alleged use of the product defined in these claims.

2. ☐ Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows :

The claims are directed to a plurality of inventive concepts as follows:

Group 1 - Claims 1-32, 34-41 (partially) are directed to methods using whey acid protein four-disulfide core domain (WFDC2) as a marker for endometrial disease and sets of markers containing the same;

(Continued on first supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

**Remark on Protest** ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2007/001935

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	HEBBAR, V. et al. "Differential Expression of MUC Genes in Endometrial and Cervical Tissues and Tumors", BMC Cancer, 2005, Vol.5, pages 124-135, eISSN 1471-2407.	1-6, 8-18, 21-31, 39-41 32, 34, 35, 37, 38
X — Y	LALITKUMAR, P.G.L. et al. "Placental Protein 14 in Endometrium During Menstrual Cycle and Effect of Early Luteal Phase Mifepristone Administration on its Expression in Implantation Stage Endometrium in the Rhesus Monkey", Hum. Reprod., 1998, Vol.13, No.12, pages 3478-3486, pISSN 0268-1161, eISSN 1460-2350.	1, 3, 4, 8, 39 38
X — Y	LI, T.C. et al. "Is the Measurement of Placental Protein 14 and CA-125 in Plasma and Uterine Flushings Useful in the Evaluation of Peri-Menopausal and Post-Menopausal Bleeding?", Hum. Reprod. 1998, Vol.13, No.10, pages 2895-2901, pISSN 0268-1161, eISSN 1460-2350.	1-6, 8-18, 21-28, 39-41 34, 35, 37, 38
X — Y	MUTTER, G.L. et al. "Global Expression Changes of Constitutive and Hormonally Regulated Genes During Endometrial Neoplastic Transformation", Gynecol. Oncol., 2001, Vol.83, No.2, pages 177-185, pISSN 0090-8258, eISSN 1095-6859.	1-5, 7-18, 21-28, 39-41 34, 35, 37, 38
X — Y	WO 02/09573 A2 (MUTTER, G.L. [US]) 7 February 2002.	1-5, 8-28, 39-41 34, 35, 37, 38
X — Y	DESOUZA, L. et al. "Proteomic Analysis of the Proliferative and Secretory Phases of the Human Endometrium: Protein Identification and Differential Protein Expression", Proteomics, 2005, Vol.5, No.1, pages 270-281, pISSN 1615-9853, eISSN 1615-9861.	1, 3, 4, 8, 39 38
Y	WO 2005/061725 A1 (COLGAN, T.J. [CA/CA]) 7 July 2005.	32, 34, 35, 37, 38
Y	DESOUZA, L. et al. "Search for Cancer Markers from Endometrial Tissues Using Differentially Labeled Tags iTRAQ and cICAT with Multidimensional Liquid Chromatography and Tandem Mass Spectrometry", J. Proteome Res., 2005, Vol.4, No.2, pages 377-386, pISSN 1535-3893, eISSN 1535-3907.	32, 34, 35, 37, 38
X, P	ABDUL-RAHMAN, P.S. et al. "Expression of High Abundance Proteins in Sera of Patients with Endometrial and Cervical Cancers: Analysis Using 2-DE with Silver Staining and Lectin Detection Methods", Electrophoresis, June 2007, Vol.28, No.12, pages 1989-1996, pISSN 0173-0835.	1-6, 8-18, 21-26, 29, 39-41
X, P	WO 2007/081767 A2 (MOORE, R. [CA/US]) 19 July 2007.	1-6, 8-18, 21-26, 29, 39-41
(Continued on next page)		

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2007/001935

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FERGUSON, S. E. et al "Stratification of Intermediate-Risk Endometrial Cancer Patients into Groups at High Risk or Low Risk for Recurrence Based on Tumor Gene Expression Profiles", 2005, Clin. Cancer Res., Vol.11, No.6, pages 2252-2257, pISSN 1078-0432.	1-41
A	REID-NICHOLSON, M. et al. "Immunophenotypic Diversity of Endometrial Adenocarcinomas: Implications for Differential Diagnosis", Mod. Pathol., August 2006, Vol.19, No.9, pages 1091-1100, pISSN 0893-3952, eISSN 1530-0285.	1-41

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.  
**PCT/CA2007/001935**

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO 0209573A2	07-02-2002	US 6773883B2	10-08-2004
		US 2002106662A1	08-08-2002
		WO 0209573A3	01-08-2002
WO 2005061725A1	07-07-2005	AU 2004303448A1	07-07-2005
		CA 2550900A1	07-07-2005
		EP 1711618A1	18-10-2006
WO 2007081767A2	19-07-2007	EP 1846768A2	24-10-2007
		US 2007286865A1	13-12-2007
		WO 2007081768A2	19-07-2007

## Continuation of Classification Symbols

*C07K 14/81* (2006.01) , *C12N 9/12* (2006.01) , *C12Q 1/00* (2006.01) , *C12Q 1/68* (2006.01) ,  
*C40B 30/00* (2006.01) , *C40B 30/04* (2006.01) , *G01N 33/53* (2006.01) , *G01N 33/574* (2006.01)

## Continuation of Box No. III

Group 2 - Claims 1, 3, 4, 8, 29-32, 34-39 (partially) and 33 (completely) are directed to methods using whey acid protein four-disulfide core domain (WFDC2) as a marker for endometrial phase and sets of markers containing the same;

Groups 3, 5, 7, 9, and 11 - Claims 1-32, 34-41 (partially) are directed to methods using clusterin (Group 3), mucin 5B (Group 5), leucine aminopeptidase 3 (Group 7), gelsolin-like capping protein (Group 9) or progesterone-associated endometrial protein (Group 11) as a marker for endometrial disease and sets of markers containing the same; and

Groups 4, 6, 8, 10 and 12 - Claims 1, 3, 4, 8, 29-32, 34-39 (partially) are directed to methods using clusterin (Group 4), mucin 5B (Group 6), leucine aminopeptidase 3 (Group 8), gelsolin-like capping protein (Group 10) or progesterone-associated endometrial protein (Group 12) as a marker for endometrial phase and sets of markers containing the same.

The claims must be limited to one inventive concept as set out in Rule 13 of the PCT.

An a posteriori analysis has concluded that biomarkers associated with endometrial cancer are known in the art and thus cannot serve as a novel and inventive feature uniting the subject matter of the instant application. Individual markers (Galgano et al; Zierau et al; Hebbar et al; Li et al), lists of markers that exhibit altered expression levels in endometrial cancer (WO 02/09573; Mutter et al; Desouza et al, J. Proteome Res.; WO 2005/061725 ), and true combinations of markers where the diagnostic value of the combination is superior to that of the individual markers (Ferguson et al; Reid-Nicholson et al) have been previously described. In view of the aforementioned prior art documents, each endometrial marker or specific combination of markers is to be assessed as an independent alleged invention.

Further, endometrial phase markers are known in the art (Ace et al; Lalitkumar et al; Desouza et al, Proteomics, 2005). A given endometrium-associated marker that serves as an endometrial cancer biomarker does not necessarily serve as an endometrial phase biomarker and vice versa. It follows that, because being an endometrial phase biomarker is independent of being an endometrial cancer biomarker, the utility of the claimed biomarker is another basis for the division of the subject matter of the instant claims.